Oxidation of Two 2,6-Di-*tert*-butyl-substituted Phenols with Quaternary Alkylammonium Hexacyanoferrate(III) Salts

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A method is described for the oxidation of phenols with tetrabutylammonium hexacyanoferrate(III). The oxidant was tested with two 2,6-di-*tert*-butyl-substituted phenols. For comparison, the same phenols were oxidized in methanol with hydrogen hexacyanoferrate(III). With the latter oxidant, quinones and quinol ethers were formed. Oxidation with the former, less acid, oxidant gave products that were formed *via* quinone methide intermediates. The results suggest that a change in mechanism from radical to ionic occurs when going from a less acid to a more acid system.

In a recent report Taimr and Pospíšil [1] pointed out the possibility of using hydrogen hexacyanoferrate(III) for the oxidation of some phenols. The use of this oxidant is limited by its insolubility in organic solvents other than alcohols and by its high acidity. In order to find a less acid system which would be soluble in non-polar solvents the acid was converted to its tetrabutylammonium salt by ion-pair extraction.[2] The usefulness of this salt as an oxidant was tested on some sterically hindered alkyl phenols.

RESULTS

The ion-pair extraction yielded a chloroform-soluble, light green powder with the formula $(Bu_4N)_3Fe(CN)_6$ indicated by iodometric titration. No oxidation was observed when 2,6-di-*tert*-butyl-4-methylphenol (*1*) was treated with this compound in chloroform solution at room temperature even for several days. *p*-Toluenesulfonic acid was added to the solution in order to alleviate the steric hindrance of the bulky tetraalkylammonium groups and to provide counter-ions for the tetravalent hexacyanoferrate(II) anion. Oxidation of *1* started when two equivalents of *p*-toluenesulfonic acid had been added. Solutions containing $(Bu_4N)_3Fe(CN)_6$ and *p*-toluenesulfonic acid in a molar ratio of 1:2, were found to be useful for the oxidation of phenols. The oxidant in these solutions was taken to have the composition $Bu_4NH_2Fe(CN)_6$. Compound *1* in chloroform was oxidized to 3,3′,5,5′-tetra-*tert*-butyl-4,4′-dihydroxybibenzyl (*2*).

The oxidation of *1* was repeated in methanol solution to compare the new oxidant with the more acidic hydrogen hexacyanoferrate(III). In the oxidation with $H_3Fe(CN)_6$ we were able to reproduce the results of Taimr and Pospíšil:[1] in a combined yield of 30 %, the quinol ether *3*

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7
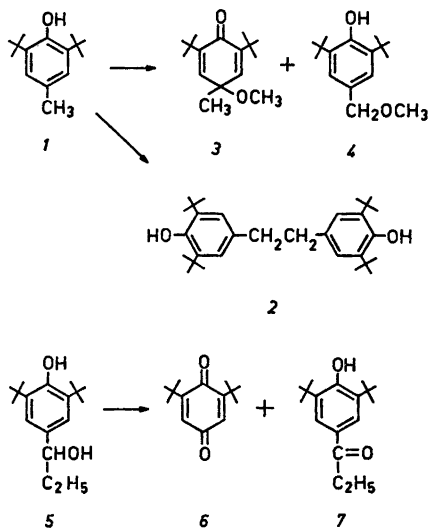
and the benzyl methyl ether *4* were formed roughly in the proportions 9 to 1. The formation of the quinol ether *3* is kinetically controlled: extensive isomerization of *3* to *4* occurred when the oxidation time was extended from 1 to 25 h. This isomerization reaction is the subject of further investigation.

In the oxidation with $Bu_4NH_2Fe(CN)_6$ the same two compounds were formed but in inverse proportions, the benzyl methyl ether *4* being the main product. A similar change in reaction path with change in acidity was observed with the substituted benzyl alcohol *5*. High acidity leads to loss of the side-chain and formation of the 1,4-quinone *6*, lower acidity favours the formation of the ketone *7*.

DISCUSSION

Although there is at present insufficient evidence to confirm the mechanism of these reactions, the change in product composition with change in acidity suggests two different mechanisms for the two cases. Waters has recently suggested [3] that the pH of the reaction medium can influence the reaction mechanism in phenol oxidations. Thus a low pH favours the formation of phenoxonium ions instead of the phenoxy radicals which predominate in neutral and alkaline solutions.

Application of this concept to the present reactions would give the following two mechanisms.

At high acidity the phenol is oxidized to a phenoxonium ion which reacts with the nucleophilic solvent to form a cyclohexadienone (Scheme 1). This reaction has been observed in the anodic oxidation of *1* in acetonitrile containing methanol,[4] and has been shown to be a two-electron oxidation.[5] In the case of the benzyl alcohol *5*, the intermediate quinol ether will be unstable under acid conditions, the side-

chain splitting off as propionic aldehyde.[6] The resulting *p*-methoxyphenol has a lower redox potential than the starting material[7] and is rapidly oxidized further to 2,6-di-*tert*-butyl-*p*-benzoquinone.

At low acidity the formation of phenoxonium ion is retarded in favour of the disproportionation of the phenoxy radical. Phenoxy radicals from sterically hindered phenols having benzylic hydrogens tend to disproportionate to a quinone methide and the parent phenol. This has been demonstrated for the phenoxy radical from *1*.[8,9] The decay of the radical has been studied kinetically,[8] and the results are consistent with a mechanism which involves the reaction between two phenoxy radicals. Products formed *via* a quinone methide have been identified.[8c,9] When the radical from *1* disproportionates in methanol the quinone methide intermediate adds methanol to form the benzyl methyl ether *4*.[9] A similar disproportionation of the phenoxy radical from *5* would give a quinone methide which is a tautomer of the ketone *7* (Scheme 2).

The implication of these results is that the concept[3] of a competition between radical and ionic mechanisms offers a partial explanation for the often confusing variety of products encountered in phenol oxidations.
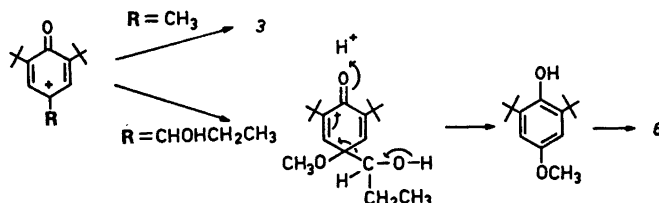
EXPERIMENTAL

NMR-spectra. 60 MHz in $CDCl_3$, tetramethylsilane as internal standard, δ-values.
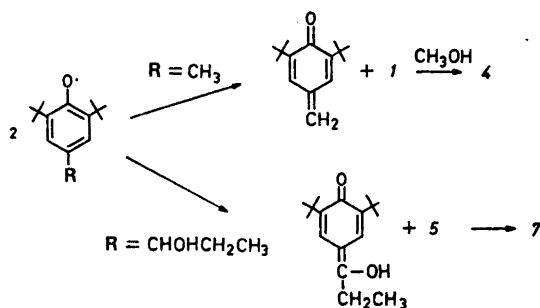
Preparative TLC. The products were separated on 2 mm precoated TLC-plates (Merck PSC F 254) with ethyl acetate-cyclohexane (1:15) as eluent.

Materials

2,6-Di-tert-butyl-4-methylphenol. Fluka AG.
2,6-Di-tert-butyl-4-(1-hydroxypropyl)phenol (5). Prepared from ethyl magnesium bromide

Scheme 1.

Scheme 2.

and 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde,[10] m.p. 74 — 76 °C (Lit.[11] 77 °C).

Hydrogen hexacyanoferrate (III). The acid was precipitated from an aqueous solution of potassium hexacyanoferrate(III) with an excess of concentrated hydrochloric acid.[1]

Tri-(tetrabutylammonium)hexacyanoferrate- (III). An aqueous solution of hydrogen or potassium hexacyanoferrate(III) was made alkaline with an excess of tetrabutylammonium hydroxide and extracted with chloroform. The chloroform extract was washed with water and dried (CaSO$_4$). Evaporation yielded a pale green powder for which iodometric titration gave an equivalent weight of about 960 (Calc. for C$_{54}$H$_{108}$N$_9$Fe: 938)

Tetrabutylammonium dihydrogen hexacyanoferrate(III). The above preparation was dissolved in chloroform or methanol, and *p*-toluenesulfonic acid (2 equiv.) was added. The solution was used as such for oxidations.

Oxidations

Compound 1 in chloroform. 1.97 g (2.1 mmol) of tetrabutylammonium hexacyanoferrate(III) and 4.2 mmol of *p*-toluenesulfonic acid was added to 220 mg (1 mmol) of *1* dissolved in dry chloroform. After standing overnight at room temperature diethyl ether and water were added, the ether layer was washed with water and dried. Evaporation left 276 mg of product which yielded 36 mg pure 3,3′,5,5′-tetra-*tert*-butyl-4,4′-dihydroxybibenzyl (*2*) on preparative TLC. M.p. 170 — 171 °C (Lit.[8] 170.0 — 170.5 °C). NMR (CDCl$_3$): δ 1.42 (36 H, s, *t*-Bu), 2.83 (4 H, s, Ar — CH$_2$ —), 5.00 (2 H, s, ArOH), 6.99 (4 H, s, ArH).

Compound 1 in methanol with H$_3$Fe(CN)$_6$. The procedure described by Taimr and Pospíšil was followed. Separation of the reaction mixture by preparative TLC gave 20 — 30 % of 2,6-di-*tert*-butyl-4-methyl-4-methoxy-2,5-cyclohexadienone (*3*) m.p. 90 — 91 °C (Lit.[1] 93 °C). NMR CCDCl$_3$: δ 1.25 (18 H, s, *t*-Bu), 1.37 (3 H, s, CH$_3$), 3.12 (3 H, s, OCH$_3$), 6.45 (2 H, s, ring

protons). In addition, between 2 and 3 % of *4* was isolated in the different runs.

Compound 1 in methanol with Bu$_4$NH$_2$Fe- (CN)$_6$. To 1 mmol of *1* in methanol was added 2.1 mmol of tetrabutylammonium hexacyanoferrate(III) and 4.2 mmol of *p*-toluenesulfonic acid. After 1 h at room temperature the products were precipitated with water, extracted with ether and separated on preparative TLC. 39 — 42 % of unreacted *1* was recovered. The rest was a mixture of *3* and *4* in proportions (determined from NMR-spectra and by weighing the TLC fractions) which varied between 1:6 and 1:10 in different runs, the main product being 2,6-di-*tert*-butyl-4-(methoxymethyl)-phenol (*4*). NMR (CDCl$_3$): δ 1.44 (18 H, s, *t*-Bu), 3.34 (3 H, s, OCH$_3$), 4.29 (2 H, s, ArCH$_2$), 5.14 (1 H, s, ArOH), 7.1 (2 H, s, ArH).

Compound 5 in methanol with H$_3$Fe(CN)$_6$. To 264 mg (1 mmol) of *5* in methanol was added 450 mg (2.1 mmol) of H$_3$Fe(CN)$_6$ in methanol. After 1 h at room temperature the products were precipitated with water and extracted with ether. Preparative TLC gave two products: 2,6-di-*tert*-butyl-1,4-benzoquinone (56.4 mg), m.p. 66 — 67 °C (Lit.[12] 66.5 — 68 °C) and 3,5-di-*tert*-butyl-4-hydroxyphenyl ethyl ketone (*7*) (4.0 mg). The ketone was identified by comparison with material synthesized by oxidation of *5* with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, m.p. 137 °C (Lit.[11] 137 °C).

Compound 5 in methanol with Bu$_4$NH$_2$Fe- (CN)$_6$. To 52.8 mg (0.2 mmol) of *5* in methanol was added 394.8 mg (0.4 mmol) of tetrabutylammonium hexacyanoferrate(III) and 145.5 mg (0.8 mmol) of *p*-toluenesulfonic acid. After 1 h at room temperature TLC showed an almost quantitative conversion to 3,5-di-*tert*-butyl-4-hydroxyphenyl ethyl ketone (*7*). NMR (CDCl$_3$): δ 1.18 (3 H, t, H$_\beta$), 1.43 (18 H, s, *t*-Bu), 2.92 (2 H, q, H$_\alpha$), 5.70 (1 H, s, AtOH), 7.81 (2 H, s, ArH). $J_{\alpha\beta} = 7.0$ Hz.

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